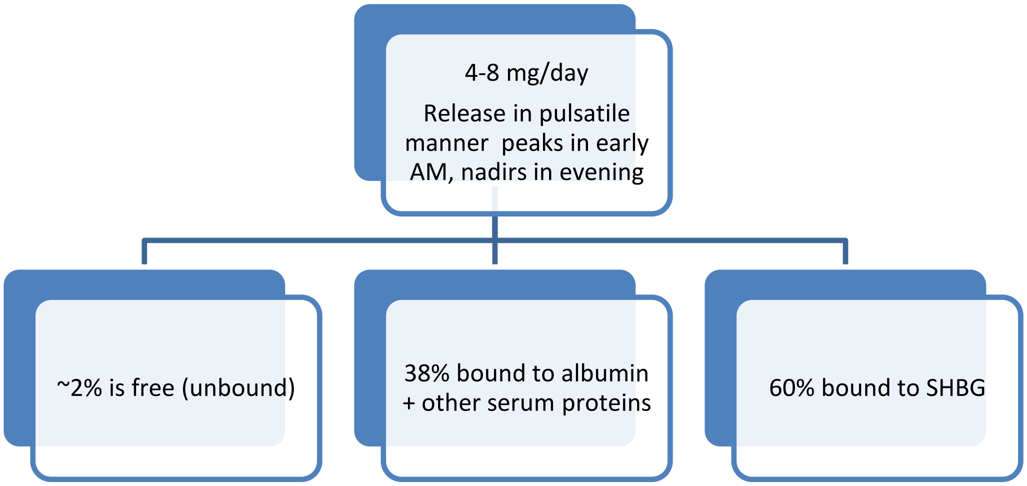
Male hypogonadism

Physiology

Immediately after birth, serum testosterone levels reach adult concentrations over several months. Thereafter and until puberty, testosterone levels are low, thus preventing male virilisation.

Puberty starts with the production of gonadotrophins, initiated by GnRH secretion from the hypothalamus and resulting in testosterone production, male sexual characteristics and spermatogenesis.

testosterone is normally produced by men


4-8 mg/day
Release in pulsatile manner peaks in early AM, nadirs in evening
~2% is free (unbound)
38% bound to albumin + other serum proteins
60% bound to SHBG

factors that affect SHBG production in the liver

increase SHBG levels (less bioavailable T)	decreaseSHBG (more bioavailable T)
• elevated estrogen • high T4 • aging • cirrhosis • anti-convulsants • HIV infection	• exogenous androgens • GH • obesityDefinition

Male hypogonadism

Definition

It is a clinical syndrome characterised by impaired testicular function, which may affect spermatogenesis and or testosterone synthesis which may adversely affect multiple organ functions and quality of life

Epidemiology

Androgen deficiency increases with age; In middle-aged men, the incidence was found to be 6%

Etiology

It can be classified accordance into :

a. **Secondary hypogonadism as "endocrine cause of infertility"**

Central defects of the hypothalamus or pituitary resulting in impairment of pituitary LH and FSH secretion cause secondary testicular failure.

b. **primary hypogonadism** as testicular cause of infertility

Primary testicular failure results in low testosterone levels, impairment of spermatogenesis and elevated gonadotrophins.

c. **Male hypogonadism due to mixed dysfunction of hypothalamus/pituitary and gonad**

This form was named late-onset hypogonadism some years ago

d. **Male hypogonadism due to defects of androgen target organs**

There are androgen receptor defects with complete, partial and minimal androgen insensitivity syndromeas well as 5α-reductase deficiency

Diagnosis

It is determined by the age of onset and the severity of hypogonadism.

1. Foetal androgen deficiency

androgen deficiency during the first 14 weeks of gestation, may result in abnormal genital development, ranging from hypospadias to female external genitalia with intra-abdominal testis.

Presentation

- at an early age because of clearly abnormal external genitalia.
- during puberty because of delayed pubertal development in phenotypic men or primary amenorrhoea in XY women

2. Prepubertal onset of androgen deficiency

At the start of puberty, rising gonadotrophin levels result in increasing activation of spermatogenesis and testosterone secretion. rising testosterone levels result in

- the development of male secondary sex characteristics,
- comprising deepening of the voice,
- development of terminal body hair,
- stimulation of hair growth in sex-specific regions, facial hair,
- increasing penile size, enlargement of the testis
- increase in muscle mass and bone size and mass,
- growth spurt induction and eventually closing of the epiphyses.
- psychosexual effects, including increased libido.

Delayed puberty is defined as an absence of testicular enlargement at the age of 14.

Delayed puberty does not necessarily indicate the presence of a disease. The major challenge is to differentiate the condition from a constitutional delay in puberty and to determine when to start androgen treatment.

Signs and symptoms suggesting prepubertal-onset hypogonadism

- Small testes
- Cryptorchidism
- Gynaecomastia
- High voice
- Unclosed epiphyses
- Linear growth into adulthood
- Eunuchoid habitus
- Sparse body hair/facial hair
- Infertility
- Low bone mass
- Sarcopenia
- Reduced sexual desire/activity

3. Late-onset hypogonadism

It is defined as hypogonadism in a person who has had normal pubertal development and as a result developed normal male secondary sex characteristics.

Symptoms “non spesific”

- loss of libido,
- erectile dysfunction,
- sarcopenia,
- low bone mass,
- depressive thoughts,
- fatigue,
- loss of vigour,
- loss of body hair,
- hot flushes
- reduced fertility

Most of these symptoms are reminiscent of normal aging and can also be found in men with completely normal testosterone levels so they are non-specific, and confirmation of a clinical suspicion by hormonal testing is mandatory.

Recommendations

- The diagnosis of testosterone deficiency should be restricted to men with persistent symptoms suggesting hypogonadism
- Total testosterone assessment and LH should be repeated at least on two occasions
- Total testosterone levels close to the lower normal range (8-12 nmol/L), the free testosterone level should be measured .
- Suspected or known abnormal sex hormone-binding globulin (SHBG) levels, free testosterone should be included

INDICATIONS AND CONTRAINDICATIONS FOR TREATMENT

Testosterone replacement therapy (TRT) provides several benefits in relation to body composition, metabolic control and psychological and sexual parameters

Indications for testosterone treatment

- Delayed puberty (idiopathic, Kallmann syndrome)
- Klinefelter syndrome with hypogonadism
- Sexual dysfunction and low testosterone
- Adult men with consistent and preferably multiple signs and symptoms of hypogonadism
- Hypopituitarism
- Testicular dysgenesis and hypogonadism
- A decline in muscle mass and strength
- Reduced bone mineral density at the lumbar spine

Preparation

Short-acting preparations may be preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed and treatment can be discontinued if needed.

Preparation	Rout &does	Advantages	Disadvantages
Testosterone undecanoate “most widely used and safest”	oral 2cap /6h	• Don’t causes testosterone levels above the mid-range → infrequently side effects • Absorbtion through lymphatic with reduce liver involvement	resorption depends on simultaneous intake of fatty food.
Testosterone undecanoate	LA intramuscular / 3month .	Uniform T level without fluctuation	LA→can’t withdrawel if complications appear
Testosterone cypionate and Testosterone enanthate	short-acting intramuscular/2-3 wks	Possible withdraw if side effect appear	fluctuations in serum testosterone الوحيد هو واخوه
Transdermal testosterone	skin patches or gel/ day daily interval	Uniform T level without fluctuation for 24 hours	skin irritation at the site of application (patches) and risk of interpersonal transfer (gel)
Sublingual and buccal testosterone	daily administration	rapid absorbtion uniform physiological testosterone level	Local irritation and pain
Subdermal depots	implanted every 5-7 months	Long duration No fluctuation in T level	infections and extrusions

Hypogonadism and fertility issues

Exogenous testosterone reduces endogenous testosterone production by negative feedback. If hypogonadism coincides with fertility issues, hCG treatment should be considered..

Does : 1500-5000 IU administered intramuscularly or subcutaneously twice weekly.

In patients with secondary hypogonadism, hCG treatment is combined with FSH treatment (usually 150 IU three times weekly i.m. or s.c.) to induce spermatogenesis

RISK FACTORS IN TESTOSTERONE TREATMENT

1- Male breast cancer

Testosterone is contraindicated in men with a history of breast cancer

2- Prostate cancer

PSA testing and digital examination of the prostate before and during therapy are highly recommended.

Testosterone therapy is clearly contraindicated in men with prostate cancer. However , there is debate involves the use of TRT in hypogonadal men with a history of prostate cancer and no evidence of active disease. treatment should be restricted to,

- patients with a low risk.
- Therapy should not start before 1 year of follow-up after surgery or brachytherapy or external-beam radiotherapy (EBRT)
- there should be no PSA recurrence .

3- Cardiovascular diseases

increase in red blood cells is a common side effect of testosterone. Haemoglobin and haematocrit measurements are recommended before treatment and periodically thereafter

Testosterone treatment is not related to the development of de novo cardiovascular events however Patients with erythrocytosis and serious congestive heart failure testosterone therapy should be discontinued until the resolution of congestive heart failure

4- Obstructive sleep apnoea

There is no evidence correlating TRT with obstructive sleep apnoea (OSA)onset or worsening T

5- high dose T can lead to hepatic toxicity

- hepatitis
- cholestatic jaundice
- hepatocarcinoma
- hepatomas
- hemorrhagic liver cysts

Follow up of pt on TRT at 3, 6 and 12 months and thereafter annually by

1- changes in the clinical manifestations of testosterone deficiency
2- Testosterone level
    - There are no define optimal serum levels
    - TRT should restore the serum testosterone level to the mid-normal range of specific age groups of men
3- Haematocrit
4- Prostate examination by digital rectal examination and PSA
5- Bone mineral density (BMD)
    - only in men whose BMD was abnormal before initiation of TRT.
6- Cardiovascular system
    - Routine assessment is not indicated , it is indicated only in men with cardiovascular co-morbidity before and during TRT

Recommendations الخلاصه

- Haematological, cardiovascular, breast and prostatic assessment should be performed before the start of treatment.

- Haematocrit and haemoglobin monitoring, PSA and digital rectal examination of prostate and breast examination are recommended assessments during TRT therapy.

- In patients operated on for localised prostate cancer, testosterone therapy should not start before 1 year of follow-up without PSA recurrence has been completed.

- Contraindications against testosterone treatment
    - Prostate cancer
    - PSA > 4 ng/mL
    - Male breast cancer
    - Male infertility
    - Haematocrit > 50%
    - Severe sleep apnoea????
    - Severe lower urinary tract symptoms due to benign prostatic hyperplasia